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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BERCH, MARK L	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 11/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/603,503	NESTOR ET AL.	
	Examiner	Art Unit	
	Mark L. Berch	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/16/2004 has been entered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 23-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S.P. 5,043,339.

Note Formula I in U.S.P. 5,043,339, since one of R and R^1 must be an amino acid, the genus describes basically mono- and diesters (depending on whether 1 or both of R, R^1 are amino acids). The preferred amino acids are listed at column. 2, lines 23 as glycine, alanine, valine, and isoleucine. This also happens to be the only amino acids used in the examples. Both mono and diesters are prepared; See Ex. 6. This than gives 8 choices; four monoesters and 4 diesters. There are 2 preferred choices for B, cytosine, and ganciclovir (column. 2, line 14). Again, these are the two bases of the examples.

This then produces 8 X 2=genus of 16. The claims are limited to the HCl salt. 9 acids are named, including HCl. This constitutes a genus then of 16 x 9 = 144 compounds. A genus of that size renders all of the embraced species obvious. Note *Merck & Co vs. Biocraft*, 10 USPQ 2nd 1843, 1846 in which a reference disclosing "more than 1200 combinations", with no indication that any one of them was preferred over the others, was found to render each choice obvious. Note also *In re Corkill*, 226 USPQ 1005, 1008 (where the genus was "thousands") and *In re Susi*, 169 USPQ 423, 425, (where the genus of the Lauer reference was called "huge"; it unquestionably embraced in excess of 10,000 compounds) with similar fact patterns.

With regard to the CMV of claims 25-26, note column 2, line 43 which states "particularly CMV", and human use appears on the same line, for claim 28. The oral administration of claims 24 and 27 is discussed in detail at column 4, lines 3-11.

In the parent, paper of 8/13/02, page 12, applicants performed a calculation and arrived at a total of 486. While the reference possibly teaches a genus of that size, it also teaches a smaller genus. A reference is available for all that it teaches, see *In re Lamberti*, 192 USPQ 278, 280; *In re Boe,* 148 USPQ 507, 510; *In re Fracalossi*, 215 USPQ 569, 570. The fact that a reference teaches a genus A does not detract from a teaching of a subgenus A'. Specifically, while it is true that 9 amino acids are named, there is also a teaching of four preferred amino acids, at column 2, line 23. The fact that the broader list exists does not detract from the narrower list. It is not impermissible hindsight to use a subgenus of 4 which the reference clearly labels as preferred. Use of the 4 instead of the 9 in this calculation gives a genus of 216.

In addition, the use of "3" (types of esters) in the third line is not believed to be correct. The reference describes two types of esters: the mono ester, and the diester. Thus, there is the mono glycine ester, the di-glycine ester, the mono-valine, the di-valine, etc. The use of the correct 2 in place of 3 will give the correct figure of 144. Applicants comments on page 13 are not agreed with in this regard. There is nothing in the reference to point to mixed esters. The method given in the reference would not make a mixed ester.

In the paper of 1/3/03 of the parent, applicants did a new calculation and arrived at 648. However, using either of these numbers, this is still below the 1200. Applicants presented no reasoning why a genus of "more than 1200 combinations" in *Merck* would render each choice obvious, and yet a substantially smaller number would not render each choice obvious in this case. Similarly, in *In re Corkill*, 226 USPQ 1005, 1008, there was a selection made "from among 'thousands' of compounds" and yet it was still held obvious. Likewise, in *In re Susi*, 169 USPQ 423, 425, the court noted of the Lauerer reference used, "As appellant points out, Lauerer's disclosure is huge....." And still, obviousness was found to be present.

In the newest paper, applicants present a fresh set of calculations, this time arriving at the sum of "at least 576 or 1818." Further, by using "the 46 acids Applicants have listed" (i.e. those appearing "at paragraph 0066" (actually, paragraph 0054) of this application) rather than the ones that are in the actual reference, they arrive at 2944 or 9292. However:

I. Even if the highest number tendered, 9292 is used, that is smaller than the genus in the Lauer reference of *Susi*.

II. The use of the 46 acids from this application is illegitimate. Only 9 acids are named in the reference, period. As the remarks themselves state, "...the genus or subgenus must be as stated in the reference, not constructed ad hoc after the fact."

III. With regard to the above issue of the mixed esters (one OH esterified with one acid, and the other with a different acid), applicants argue that Beauchamp could have prepared the monoester with one acid, and then reacted that with a different acid. But there is no mention of any such procedure, or any other procedure, for obtaining a mixed ester. The reference simply does not specifically point in any form to the concept of a mixed ester.

IV. Applicants reach their large numbers by increasing the amino acids far beyond those recited in the specification. Only four are named, yet applicants' calculation includes many more, including those which are not even aliphatic. However, this argument fails to overcome the central point that the reference teaches the narrow genus which arises when one uses simply those amino acids which are actually named. The fact that there is a genus of 576 or 1818 does not detract for the fact that there is also a clearly discernable genus of 144. As a general rule, the fact that there is material in a reference which fails to render clams obvious does not negate teachings which do render claims obvious. For example, many if not most references which have a species which renders a claim obvious also have a genus which is so large (e.g. in the millions) which does not render the claim obvious. The presence of the larger does not negate the effect of the smaller.

Applicants next discuss this reference in the context of the Beauchamp (1992) reference. That has nothing to do with this rejection. The rejection is based on what

U.S.P. 5,043,339 itself teaches. Regardless of what appears in Beauchamp (1992), the patent still teaches what it teaches. The inferences that one would draw from Beauchamp (1992) (which, as noted in the other rejection, the examiner does not at all agree with) cannot subtract material from what the patent has. A reference teaches what it does regardless of later events: "The information conveyed by prior art is crystallized as of the date it is made public and the crystals cannot be corrected or altered to convey information or facts *later* acquired by others skilled in the art." *Pfizer, Inc. v. International Rectifier Corp. et al.* 207 USPQ 397, 425 (emphasis in original). Thus, this argument has no legal merit. Furthermore, applicants are clearly reading more into the Beauchamp (1992) reference than is justified. Finally, the argument of 8-fold being beter than 5-fold again goes to the question of the di-valinate, which, as set forth many times, is not the basis of either rejection. The arguments based on the declaration are unpersuasive here as well, for reasons set forth below.

Claims 23-28 are rejected as obvious, 35 U.S.C. 103 over Verheyden in view of Beauchamp (1992).

The claimed species is the monovalinate ester of Ganciclovir, as the HCl salt. The reference teaches Ganciclovir, and the HCl salt is named at column 2, line 64.

With regard to the use of CMV of claims 25-26, note column 3, line 16 which names CMV. Human use for claim 28 is disclosed at column 3, line 35. The oral administration of claims 24 and 27 is exemplified in example 4D in column 8, lines 55-68 and also at column 3, lines 37-47. With regard to the physical characteristics recited in claim 29, note the discussion in the above rejection.

Ganciclovir is extremely similar in structure to Acyclovir, and both are antivirals used against Herpes viruses. Their structures are indeed identical, except that Acyclovir has one hydroxy methyl attached to the methoxy methyl side chain and Ganciclovir has two. Both are antivirals used to treat herpes infections. Hence, one skilled in the art would find it reasonable to infer information from one about the other. The difference is so small (one hydroxymethyl versus two) that if these are not analogous, then what is? The entire rest of the molecule, as well as the utility, is the same. A secondary reference is always going to have some structural difference, otherwise the secondary reference will itself anticipate.

Beauchamp (1992) teaches that of all the amino acid prodrugs tested with Acyclovir, the L-valyl ester "was the best prodrug". It gave 63% urine availability as opposed to 19% for the non-esterified drug. One skilled in the art would be motivated to obtain this enormous improvement with Ganciclovir too by preparing the L-valyl ester of ganciclovir in order to obtain a comparable improvement. Thus, the secondary reference provides abundant motivation to prepare this exact L-valyl ester.

Further with regard to hydrochloride, Method A of the secondary reference gave the salts as hydrochlorides (see page 159, column. 1, 14th from last line).

The traverse, presented in the parent, paper of 8/13/02, was unpersuasive. The question of whether Acyclovir and Ganciclovir have the exact same profile of actions, or whether adenosine and Psicofuranine have different properties is not the point. The only issue here is whether the Beauchamp (1992)'s teaching that it is extremely advantageous to convert Acyclovir to its valinate ester would motivate one of ordinary skill in the art to do the same for a compound (Ganciclovir) of very similar structure and

identical utility. Even the Crumpacker reference cited by applicants calls Acyclovir an "analogue" of Ganciclovir (page 721, column 1 second full paragraph). Moreover, the antiviral mechanism of the two drugs is the same. As Crumpacker teaches, both drugs are converted to the triphosphate, and that triphosphate is, in both cases, an inhibitor of CMV DNA polymerase. The fact that Ganciclovir is not also "an absolute chain terminator" hardly prevents these two references from being combinable. This argument is made for completeness only; the examiner notes that at present, this argument is no longer being relied on.

Next, applicants argued in that paper, and again in the paper of 9/16/2004 that applying the teaching of the secondary reference would give the bis ester, rather than the mono ester. The bis-ester is probably also obvious, but that is not the issue here, only whether the mono-ester would be obvious. The fact that the bis-ester is obvious does not make the mono-ester non-obvious. The compounds of Beauchamp (1992) are all monoesters, so one simply cannot argue that monoesters are not an obvious form. Applicants thus argue that the reference teaches "that all free hydroxyl groups should be esterified". However: 1) technically, this is not true. There is another OH at the 6 position. This is not esterified. 2) Even if understood as all OH at the 9-position substituent, this is simply an artifact of the circumstance that the secondary reference has only one OH, so that esterifying one esterifies all. At all rate, monoesterification is what the secondary reference teaches as producing the excellent results, and therefore, monoesterification is deemed an obvious choice.

The remarks point to the Susan Malcolm declaration. This line is unpersuasive for the following reasons:

A. Actually, applicants have presented three sets of data: The material in the specification, material in a "Memorandum of Record" submitted with the Reply Brief in the Grandparent, and material in the Susan Malcolm declaration, all different. Specifically, it is not clear why the Malcolm data is different from the data presented previously in the "Memorandum of Record". Three out of the five reported numbers are different, and all the Standard Deviations are different. The second Appeal Brief, page 11, addressed this difference, but the answers are not very specific. The remarks refer, for example to "recalculations based on purity analysis of the materials tested between the preliminary and final data reporting." It is hard to know what to make of this. Does this mean that the test was run, and then a purity analysis was performed, and the purity was not what was thought, so that the numbers were recalculated? If so, such things ought to be spelled out in the declaration, not in the remarks. The Malcolm declaration says nothing at all about purity, so one would assume that the materials tested were completely pure, which would be inconsistent with this understanding of those remarks. The most recent remarks do not address this issue, and hence this declaration cannot be relied upon.

B. Since it is only the crystalline material which is present in this application, it must be assumed that Malcolm used the crystalline material, but the claims call for the non-crystalline. Thus, it is likely that the wrong form was used.

C. The data shows expected, not unexpected differences. Acyclovir monovalinate has 53.4% bioavailability', the corresponding claimed Ganciclovir monovalinate has 55.4%. Given the fact that the exact numbers that are obtained are a rather sensitive function of the exact details as to how the test is run (as declarant sets forth in paragraph 9), such a

difference is hardly meaningful. The huge error bars given in the declaration (for example, "53.4% ± 9.40%") show clearly that this difference is NOT even close to being statistically meaningful. Preparing the Acyclovir valinate puts it into a form where just over half is bioavailable; the same has now been found true for the claimed Ganciclovir monovalinate. One would expect from the Acyclovir results just what was actually found, and hence no unexpected results are seen. Thus, while applicants point to this "53.4% for Valacyclovir vs. 55.4% for valganciclovir" as "improves the bioavailability", and an "unexpected and surprising result", the data applicants present states clearly that this difference is not statistically significant.

D. The declarant notes the 1.6 ratio between the Ganciclovir mono- and di-esters of Ganciclovir (up from the 1.5 ratio seen in the "Memorandum of Record"), and the remarks point to this again. However, as the examiner has repeatedly pointed out in the prosecution of this case, this rejection is not over the bisvalinate. It appears that an impasse has been reached on this issue, since applicants continue to point to a comparison (to the divalinate) which is just not relevant to this rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. It also lacks enablement.

Applicants have inserted a new "non-crystalline" limitation into the independent claim. This limitation lacks description in the specification. This material is prepared in Example 3, Step B (paragraph 129) and is described as crystalline. There is no specific description of the amorphous form. The remarks refer to paragraph 0146, but that material (page 47, lines 3-7) makes no mention of such a form. Hence this material is not considered enabled either, since the specification has no description of how to obtain the amorphous form rather than the crystalline form.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 23-28 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6083953. Although the conflicting claims are not identical, they are not patentably distinct from each other because the current claims are just the amorphous variation of the crystalline claims in 6083953. Applicants have not shown how these are in fact patentably distinct.

The examiner notes that a Terminal Disclaimer was filed in the parent, but that does not carry through to the daughter case; a fresh one must be filed.

Specification

Applicants may wish to consider whether their version of the specification is the same as the one at the PTO. The references to material in paragraphs 0146 and to 066 do not correspond to what the PTO has in those paragraphs.

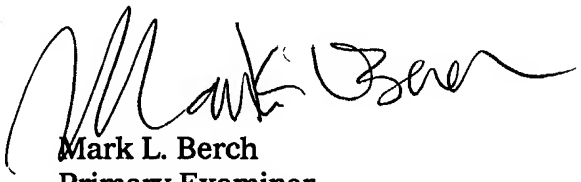
All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, THIS ACTION IS MADE FINAL even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on (571)272-0674. If you are unable to reach Dr. Shah within a 24 hour period, please contact James O. Wilson, Acting-SPE of 1624 at 571-272-0661. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9306 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0198.



Mark L. Berch
Primary Examiner
Art Unit 1624

November 22, 2004